Abdominal Aortic Aneurysm Genetic Associations: Mostly False? A Systematic Review and Meta-analysis

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Title: Abdominal Aortic Aneurysm Genetic Associations: Mostly False? A Systematic Review and Meta-Analysis

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Abstract

Background

Many associations between abdominal aortic aneurysm (AAA) and genetic polymorphisms have been reported. It is unclear which are genuine and which may be caused by type-1 errors, biases and flexible study design.

Objectives

To identify associations supported by current evidence and to investigate the effect of study design on reporting associations.

Data Sources

MEDLINE, Embase and Web of Science.

Review Methods

Reports were dual-reviewed for relevance and inclusion against pre-defined criteria (studies of genetic polymorphisms and AAA risk). Study characteristics and data were extracted using an agreed tool and reports assessed for quality. Heterogeneity was assessed using I^2 and fixed- and random-effects meta-analyses were conducted for variants that were reported at least twice, if any had reported an association. Strength of evidence was assessed using a standard guideline.

Results

Searches identified 467 unique articles, of which 97 were included. Of 97 studies, 63 reported at least one association. Of 92 studies that conducted multiple tests, only 27% corrected their analyses. Two hundred and sixty three genes were investigated

and associations were reported in polymorphisms in 87 genes. Associations in *CDKN2BAS, SORT1, LRP1, IL6R, MMP3, AGTR1, ACE* and *APOA1* were supported by meta-analyses.

Conclusions

Uncorrected multiple testing and flexible study design (particularly testing many inheritance models and subgroups, and failure to check for Hardy-Weinberg Equilibrium) contributed to apparently false associations being reported. Heterogeneity, possibly due to the case-mix, geographical, temporal and environmental variation between different studies, was evident. Polymorphisms in nine genes had strong or moderate support on the basis of the literature at this time. We make suggestions for improving AAA genetics study design and conduct.

Key words

Aortic Aneurysm, Abdominal

Genetics

Polymorphism, Single Nucleotide

Review [Publication Type]

Meta-Analysis [Publication Type]

It has been claimed that most published research findings are false and that studies of complex genetic diseases are especially prone to reporting false associations.[1] Abdominal aortic aneurysms (AAA) occur in Mendelian disorders,[2] but are usually multifactorial. Understanding AAA pathogenesis might lead to new treatments or preventive measures. No meaningful personalised genetic risk prediction[3] has been realised for AAA.

AAA is usually defined as infra-renal aortic diameter ≥30mm.[4] Using alternative definitions (infrarenal aortic diameter:suprarenal aortic diameter ratio, or comparison to predicted diameter) has striking effects on prevalence.[5] Participants may be recruited from screening programmes or surgical departments, affecting case-mix. The prevalence of old age, tobacco use and medication use has changed over time and differs between locations, so gene-environment interactions could affect results.[6-8]

Ioannidis claimed that six factors increased the likelihood of research findings being false: small study size; small effect size; multiple testing; flexible study design; financial or other interests and the 'hotness' of the field.[1] The *STrengthening the REporting of Genetic Association Studies (STREGA)* guidance aims to make reports consistent and transparent,[9] but there is variation in the analytic and statistical methods used. This study aimed to identify gene associations supported by evidence and to investigate the role of study design in reporting associations.

Methods

Search Strategy

We searched databases using MeSH terms (Table 1; Supplementary Methods) on 25 August 2014. The Medline search was simply “Aortic Aneurysm, Abdominal/ge [Genetics]”, limited to human studies. The National Institutes of Health association database, references and relevant journals were also searched.

Inclusion Criteria

- Population: cases with AAA (infrarenal aorta >30mm, infra-renal/supra-renal aortic ratio ≥1.5, surgical repair or ruptured AAA); controls were untested individuals, tested controls or hospital controls.
- Exposure: germline genomic polymorphisms.
- Comparison: disease risk in individuals with/without polymorphisms or odds of exposure in individuals with/without AAA in case-control, cross-sectional or cohort studies.
- Outcome: presence/absence of AAA.

Exclusion Criteria

Studies with single-disease controls (e.g. ischaemic heart disease), studies of somatic mutations, linkage studies and studies of AAA growth or size were excluded.

Study Selection and Data Abstraction

Two authors independently assessed titles and abstracts for relevance and full reports for inclusion. Two authors independently extracted quality and genotype/risk data for polymorphisms reported ≥2 times with an association reported at least once. Additional characteristics were abstracted by one author

Data analysis

Median study size was calculated for each year. Odds ratios for heterozygotes and homozygotes were calculated. Where genotype counts were not available, inheritance models from original reports were used. Additive model analyses were conducted using binary logistic regression in IBM SPSS Statistics v19.0 (IBM Corp, Armonk, NY), with genotypes coded as 0, 1 or 2. We re-analysed original *CRP* data from Badger *et al.*[10] to allow meta-analysis with the results of Saratzis *et al*..[11] Hardy Weinberg Equilibrium (HWE) deviation was assessed by Haldane's Exact test in *HardyWeinberg* in *R*. Sensitivity analyses excluded studies with HWE deviation (p<0.05). SNP Annotation and Proxy Search (Broad Institute, Cambridge, Massachussetts) identifed markers with r^2 >0.9. Where study data were published more than once (i.e. a study was updated or reported study populations overlapped), the selection of the report for inclusion was based on the reporting of genotype counts/frequencies or risk in preference to allelic or specific inheritance models. If the mode of reporting was the same then the larger study was included.

Heterogeneity index (I^2) and Cochrane's Q were estimated using *meta* in *R*. I^2 >50% was large, and 25-50% moderate.[12] Fixed and random effects inverse variance-weighted meta-analysis was conducted using *meta* in *R*. Significance was p<0.05 in fixed effects meta-analysis if I^2 <25% or random effects meta-analysis if I^2 ≥25%.

Results

Search results

Searches yielded 614 records. Ten were identified from other sources. There were 477 unique records. Ninety seven were included (Figure 1). Excluded studies are listed (Supplementary Table 1).

Study types and reports of associations

There were 91 candidate gene studies, four genome-wide association studies (GWAS) and two genetic risk score (GRS) studies (Table 2). Fifty six candidate studies, both GRS and all GWAS reported associations.

Study size and frequency

Median study size for a candidate gene or GRS study was 710 participants (range 91-83,024). Study size and frequency of reports increased over time (Figure 2). There was a median of three reports/year between 1994 and 25 August 2014.

Study quality

Quality indicators (Table 2) and detailed characteristics (Supplementary Table 2) are shown. Sixty two studies (64%) reported an association. Ninety two studies reported multiple tests and 25 (27%) adjusted analyses for this.

Genes investigated

Two hundred and sixty three genes were investigated (Supplementary Table 3), with 87 associated at least once. The median study size for reports that claimed an association was 811, and that of those that did not was 710 (Independent Samples Mann-Whitney U standardised test statistic=0.10, p=0.92).

Selection of polymorphisms for meta-analysis

We identified genes that featured in at least two studies and that had at least one association with sufficient data (Supplementary Table 3; Supplementary Table 4).

Results of meta-analyses

Meta-analyses are summarised (Table 3) and shown in full (Supplementary Table 5). Associations between AAA and 9p21 rs10757278, *SORT1* rs599839, *LRP1* rs1466535, *MMP3* rs3025058, *AGTR1* rs5186, *ACE* rs4646994 and *APOA1* rs964184 were supported. *CRP* rs3091244 lost significance in sensitivity analysis. *MMP2* rs243865 was associated but one of two studies deviated from HWE. Six were supported by strong evidence, three by moderate evidence and 25 had weak evidence (Table 4).

Discussion

Most studies reported associations, but only six were supported by strong evidence. Two were reported in genome-wide studies (*DAB2IP* and *LRP1*),[72,78] and four in candidate gene studies (9p21/*CDKN2BAS, IL6R*, *LPA* and *SORT1*).[50,93,94,108] There was moderate evidence for associations with *LDLR, MMP3 and AGTR1* polymorphisms. MMP3 rs3025058 was tentatively suggested to be an AAA risk factor in 1999 in a small study by Yoon *et al.* though it was not statistically significant after correction for multiple testing.[18] Subsequent studies appear to support its effect in homozygosity. Other associations currently supported by moderate or strong evidence were all made since 2008.

Inter-study inconsistency may be due to heterogeneity of effect, systematic error or bias. Multiple testing was usually uncorrected and flexible analysis was common: Many studies tested numerous inheritance models and subgroups, reporting significance when $p<0.05$. Several studies claimed HWE, but deviated significantly ($p<0.05$).[11,99]

We propose that it may be time for the genetic epidemiology research community to consider prospective registration of aetiological studies to avoid flexible *post hoc*

analyses. Simple standard steps, such as planning for adequate power, using contemporaneous controls and presenting counts and risk estimates for genotypes rather than assuming models of inheritance, checking frequencies in population databases, presenting analyses of HWE deviation and correcting for multiple testing would greatly improve the quality of reports in this field.

Our review excluded studies of aneurysm size or growth, and did not attempt to integrate results for 27 associated polymorphisms that had been reported only once.

Supported associations suggest the importance of lipoproteins. *LRP1*, *LDLR, SORT1* and the 9p21 locus affect cholesterol metabolism and atherosclerosis. *LRP1* has other important regulatory roles, including regulation of extracellular matrix breakdown by the endocytosis of proteinases.[109] *LPA* produces lipoprotein A which increases cardiovascular risk.[110] *IL6R* polymorphisms alter cardiovascular risk, possibly through inflammation.[111-114] *MMP3* affects atherosclerosis and tissue remodelling.[115] Its association in this review is in agreement with a recent meta-analysis.[116] *AGTR1* affects blood pressure, which is consistent with the association between hypertension and AAA.[6,117] *DAB2IP* is a tumour-suppressor gene involved in cell signalling, survival, migration, maturation and apoptosis.[72] Understanding their roles may help develop prevention strategies based on understanding key biological pathways. Improving future study design will avoid wasteful false associations.

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Tables

Table 1. Databases and time periods searched

Database	Date Range
Medline	1946 - August Week 1 2014
Embase	1980 – 2014 Week 33
Web of Science	All years – 25 August 2014

Table 2. Study Quality

First Author	Year	Cases (n)	Controls (n)	Ethnicity reported	Controlled for ethnicity by logistic regression	Tested or untested controls	Genotyping rate reported	HWE Reported	Multiple tests	Corr. for Multiple Testing	Study Type	Reported Association
Ramsbottom[13]	1994	82	79	Yes	No	Tested	No	No	Yes	No	Cand	No
Powell[14]	1996	232	245	Yes	No	Untested	No	No	Yes	No	Cand	No
Ramsbottom[15]	1997	85	34	No	No	Tested	No	No	Yes	No	Cand	No
Hamano[16]	1999	125	153	No	No	Tested	No	Yes	No	NA	Cand	No
Wang[17]	1999	84	51	No	No	NR	No	No	Yes	No	Cand	Yes
Yoon[18]	1999	47	174	No	No	Untested	Yes	Yes	Yes	Yes	Cand	No
Kotani[19]	2000	58	410	No	No	Untested	No	Yes	Yes	No	Cand	No
Rossaak[20]	2000	190	163	Yes	No	Untested	No	No	Yes	Yes	Cand	Yes
Pola[21]	2001	124	112	Yes	No	Tested	No	Yes	Yes	No	Cand	No
Rasmussen[22]	2001	102	118	Yes	No	Untested	No	No	Yes	No	Cand	Yes
Schillinger[23]	2002	70	61	No	No	Tested	No	No	Yes	No	Cand	Yes
Unno [24]	2002	131	106	No	No	Untested	No	Yes	Yes	No	Cand	Yes
Bown[25]	2003	100	100	Yes	No	Mixed	No	Yes	Yes	No	Cand	Yes
Jones[26]	2003	414	203	No	No	Untested	No	Yes	Yes	No	Cand	Yes
Sugimoto[27]	2003	49	237	No	No	Untested	No	No	Yes	No	Cand	Yes
Ghilardi[28]	2004	70	172	No	No	Tested	No	Yes	Yes	No	Cand	Yes
Massart[29]	2004	99	225	Yes	No	NR	No	Yes	Yes	No	Cand	Yes
Fatini[30]	2005	250	250	Yes	No	Tested	No	Yes	Yes	No	Cand	Yes
Fatini[31]	2005	250	250	Yes	No	Tested	No	Yes	Yes	No	Cand	Yes
Jones[32]	2005	428	282	No	No	Untested	No	Yes	Yes	No	Cand	No
Ogata[33]	2005	387	425	Yes	Yes	Untested	No	Yes	Yes	No	Cand	Yes
Schulz[34]	2005	133	910	Yes	No	Untested	No	No	Yes	No	Cand	No

First Author	Year	Cases (n)	Controls (n)	Ethnicity reported	Controlled for ethnicity by logistic regression	Tested or untested controls	Genotyping rate reported	HWE Reported	Multiple tests	Corr. for Multiple Testing	Study Type	Reported Association
Strauss[35]	2005	106	97	No	No	Untested	No	Yes	Yes	No	Cand	Yes
Ferrara[36]	2006	88	44	No	No	NR	No	No	Yes	Yes	Cand	Yes
Hinterseher[37]	2006	51	48	Yes	No	Untested	No	Yes	Yes	No	Cand	No
Ogata[38]	2006	387	426	Yes	No	Untested	No	No	Yes	Yes	Cand	Yes
Armani[39]	2007	146	156	No	No	Untested	No	No	Yes	No	Cand	No
Badger[40]	2007	241	1000	No	No	Untested	No	Yes	Yes	Yes	Cand	No
Bown[41]	2007	389	404	Partial	No	Tested	No	Yes	Yes	No	Cand	Yes
Deguara[42]	2007	405	405	Yes	No	Untested	No	No	Yes	No	Cand	Yes
Golledge[43]	2007	689	3538	No	No	Tested	Yes	Yes	Yes	Yes	Cand	No
Hinterseher[44]	2007	146	133	Yes	No	Untested	No	Yes	Yes	No	Cand	No
Peeters[45]	2007	88	88	No	No	Tested	No	No	No	NA	Cand	No
Waliszewski[46]	2007	112	50	Yes	No	Untested	No	No	Yes	No	Cand	Yes
Bown[47]	2008	899	815	Yes	No	Tested	No	Yes	Yes	No	Cand	Yes
Giusti[48]	2008	423	423	No	No	Tested	No	Yes	Yes	Yes	Cand	Yes
Gotting[49]	2008	129	129	No	No	Untested	No	Yes	Yes	Yes	Cand	Yes
Helgadottir[50]	2008	2836	16732	Partial	No	Mixed	No	Yes	Yes	No	Cand	Yes
Hinterseher[51]	2008	50	41	Partial	No	Untested	No	Yes	Yes	No	Cand	Yes
Jones[52]	2008	1226	1723	Partial	No	Mixed	No	Yes	Yes	No	Cand	Yes
Smallwood[53]	2008	677	656	No	No	Tested	Yes	Yes	Yes	No	Cand	Yes
Smallwood[54]	2008	678	659	No	No	Tested	Yes	Yes	Yes	No	Cand	No
Badger[55]	2009	230	279	No	No	Tested	No	No	Yes	No	Cand	No
Badger[10]	2009	248	400	No	No	Tested	No	No	No	NA	Cand	No
Elmore[56,57]	2009	950	1146	No	No	Mixed	No	No	Yes	No	GWAS	Yes
Golledge[58]	2009	1294	1460	No	No	Tested	Yes	Yes	Yes	Yes	Cand	No
Jones[59]	2009	567	552	Yes	NR	Tested	No	No	Yes	No	Cand	No

First Author	Year	Cases (n)	Controls (n)	Ethnicity reported	Controlled for ethnicity by logistic regression	Tested or untested controls	Genotyping rate reported	HWE Reported	Multiple tests	Corr. for Multiple Testing	Study Type	Reported Association
Korcz[60]	2009	133	152	Yes	No	Tested	No	Yes	Yes	No	Cand	No
Lucarini[61]	2009	201	252	No	No	Tested	No	Yes	Yes	No	Cand	Yes
Sandford[62]	2009	285	273	Yes	No	Tested	No	No	Yes	No	Cand	No
Smallwood[63]	2009	678	659	No	No	Tested	Yes	Yes	Yes	Yes	Cand	Yes
Thompson[64]	2009	741	1366	No	No	Partial	No	No	Yes	No	Cand	Yes
Atli[65]	2010	61	62	No	No	Tested	No	No	Yes	No	Cand	Yes
Baas[66]	2010	736	1024	No	No	Mixed	Yes	Yes	Yes	Yes	Cand	No
Baas[67]	2010	736	1024	No	No	Mixed	Yes	Yes	Yes	Yes	Cand	Yes
Baas[68]	2010	736	1024	No	No	Mixed	Yes	Yes	Yes	Yes	Cand	No
Badger[69]	2010	230	278	Yes	No	Tested	No	Yes	Yes	No	Cand	No
Biros[70]	2010	513	2858	No	No	Tested	No	No	Yes	No	Cand	Yes
Golledge[71]	2010	640	1071	No	No	Tested	Yes	Yes	Yes	Yes	Cand	No
Gretarsdottir[72]	2010	4559	37954	Partial	No	Mixed	No	No	Yes	Yes	GWAS	Yes
Moran[73]	2010	689	3538	No	No	Tested	Yes	Yes	Yes	No	Cand	Yes
Obukofe[74]	2010	1155	996	No	No	Tested	No	Yes	Yes	No	Cand	No
Thompson[75]	2010	1890	3785	Yes	No	Mixed	No	Yes	Yes	No	Cand	No
Biros[76]	2011	834	795	No	No	Tested	No	Yes	Yes	No	Cand	Yes
Biros[77]	2011	1904	2616	No	No	Mixed	No	Yes	Yes	Yes	Cand	No
Bown[78]	2011	6228	49182	No	Partial	Mixed	No	Yes	Yes	Yes	GWAS	Yes
Bradley[79]	2011	434	378	Yes	No	Tested	Yes	Yes	Yes	Yes	Cand	No
Hinterseher[80]	2011	874	899	No	No	NR	No	Yes	Yes	No	Cand	No
Katrancioglu[81]	2011	100	138	No	No	Tested	No	No	Yes	No	Cand	Yes
Lillvis[82]	2011	394	419	No	No	Untested	No	Yes	Yes	Yes	Cand	Yes
Roberts[83]	2011	1238	731	Yes	No	Tested	Yes	Yes	Yes	No	Cand	Yes
Bisoendial[84]	2012	613	707	No	No	Tested	No	Yes	Yes	No	Cand	No

First Author	Year	Cases (n)	Controls (n)	Ethnicity reported	Controlled for ethnicity by logistic regression	Tested or untested controls	Genotyping rate reported	HWE Reported	Multiple tests	Corr. for Multiple Testing	Study Type	Reported Association
Duellman[85]	2012	178	178	No	No	Tested	No	Yes	Yes	No	Cand	Yes
Helgadottir[50]	2012	4261	33520	Partial	No	Mixed	No	Yes	Yes	Yes	Cand	Yes
Korcz[86]	2012	300	313	No	No	Tested	No	Yes	Yes	No	Cand	No
Oszajca[87]	2012	153	152	No	No	Untested	No	Yes	Yes	No	Cand	Yes
Saracini[88]	2012	423	423	No	No	Tested	No	Yes	Yes	Yes	Cand	Yes
Antoniou[89]	2013	65	89	Yes	No	Tested	No	No	No	NA	Cand	Yes
Bradley[90]	2013	5138	39273	Partial	Partial	Mixed	Yes	Yes	Yes	Yes	GWAS	Yes
Galora[91]	2013	423	423	No	No	Tested	No	Yes	Yes	Yes	Cand	Yes
Gregorek[92]	2013	117	117	No	No	Tested	No	Yes	Yes	No	Cand	Yes
Harrison[93]	2013	4524	15710	Partial	No	Mixed	Yes	Yes	No	NA	Cand	Yes
Jones[94]	2013	7048	75976	Partial	No	Mixed	Yes	Yes	Yes	No	Cand	Yes
Tragante[95]	2013	651	2015	No	No	Untested	Yes	Yes	Yes	Yes	GRS	Yes
van 't Hof[96]	2013	859	2089	Yes	Yes	Untested	Yes	Yes	Yes	No	GRS	Yes
Wong[97]	2013	318	3930	No	No	Tested	No	Yes	Yes	No	Cand	No
Bridge[98]	2014	602	490	Yes	No	Tested	Yes	Yes	Yes	No	Cand	Yes
Cao[99]	2014	463	463	Yes	No	Tested	No	Yes	Yes	No	Cand	Yes
Duellman[100]	2014	141	168	No	No	Tested	Yes	Yes	Yes	No	Cand	Yes
Galora[101]	2014	423	423	No	No	Untested	No	Yes	Yes	Yes	Cand	Yes
Li[102]	2014	316	306	No	No	Tested	No	Yes	Yes	No	Cand	Yes
Mikołajczyk-Stecyna[103]	2014	128	180	No	No	Tested	No	Yes	Yes	No	Cand	Yes
Oszajca[104]	2014	153	152	No	No	Untested	No	No	Yes	No	Cand	Yes
Saratzis[105]	2014	797	793	Partial	No	Tested	No	Yes	Yes	No	Cand	No
Saratzis[11]	2014	722	753	Partial	No	Tested	No	Yes	Yes	No	Cand	Yes
Strauss[106]	2014	518	541	No	No	Untested	No	Yes	Yes	No	Cand	Yes

First Author	Year	Cases (n)	Controls (n)	Ethnicity reported	Controlled for ethnicity by logistic regression	Tested or untested controls	Genotyping rate reported	HWE Reported	Multiple tests	Corr. for Multiple Testing	Study Type	Reported Association
Wei[107]	2014	155	310	Yes	No	Tested	Yes	Yes	Yes	No	Cand	Yes

NR, Not Reported; NA, Not Applicable; Cand, Candidate Gene Study; GRS, Genetic Risk Score; GWAS, Genome-wide Associaiton Study

Table 3. Summary of meta-analyses

Gene and Polymorphism	OR (95% CI)	p value	I^2	FE/RE
9p21 (*CDKN2BAS*) rs10757278 Heterozygous (A/G)	1.28 (1.16-1.40)	$2.9x10^{-7}$	7.3%	FE
9p21 (*CDKN2BAS*) rs10757278 Homozygous (G/G)	1.55 (1.38-1.74)	$1.2x10^{-13}$	20.1%	FE
ACE Insertion/Deletion (rs4646994) Heterozygous (D/I)	0.90 (0.72-1.12)	0.34	66.5%	RE
ACE Insertion/Deletion (rs4646994) Homozygous (I/I)	0.67 (0.50-0.90)	$8.0x10^{-3}$	72.3%	RE
**ACE* Insertion/Deletion (rs4646994) Heterozygous (D/I)	0.85 (0.71-1.02)	0.08	48.7%	RE
**ACE* Insertion/Deletion (rs4646994) Homozygous (I/I)	0.67 (0.49-0.91)	$9.5 x10^{-3}$	75.1%	RE
AGTR1 rs5186 Heterozygous (A/C)	1.25 (1.00-1.55)	0.047	53.0%	RE
AGTR1 rs5186 Homozygous (C/C)	1.44 (1.13-1.84)	$3.5x10^{-3}$	0.6%	FE
AGTR1 rs5186 Allelic Model (C Allele)	1.19 (1.05-1.34)	$5.0x10^{-3}$	45.6%	RE
APOA1 rs964184 Additive (G allele)	1.20 (1.05-1.37)	$6.8x10^{-3}$	0.0%	FE
APOB rs1367117 Additive (A Allele)	1.09 (0.95-1.24)	0.24	50.1%	RE
CCR5 rs333 Heterozygous (WT/Del32)	1.34 (0.36-4.94)	0.66	89.5%	RE
CCR5 rs333 Homozygous (Del32/ Del32)	1.73 (0.21-14.09)	0.61	41.2%	RE
CRP rs3091244 Heterozygous (Group B)	1.58 (0.91-2.77)	0.11	87.4%	RE
CRP rs3091244 Homozygous (Group A)	2.16 (1.10-4.24)	0.03	84.0%	RE
**CRP* rs3091244 Heterozygous (Group B)	1.25 (0.68-2.30)	0.46	82.5%	RE
**CRP* rs3091244 Homozygous (Group A)	1.60 (0.79-3.22)	0.19	74.3%	RE
ELN rs2071307 Heterozygous (A/G)	0.73 (0.46-1.14)	0.16	73.5%	RE
ELN rs2071307 Homozygous (A/A)	0.90 (0.48-1.69)	0.74	77.9%	RE
HMOX1 GT(n) Repeat Heterozygous (GT(≥25)/GT(<25))	1.21 (0.25-5.85)	0.81	91.7%	RE
HMOX1 GT(n) Repeat Homozygous (GT(<25)/ GT(<25))	1.03 (0.14-7.58)	0.97	76.4%	RE
IL10 rs1800896 Heterozygous (G/A)	1.26 (0.89-1.78)	0.20	31.1%	RE
IL10 rs1800896 Homozygous (A/A)	1.59 (0.97-2.61)	0.06	53.7%	RE
LRP1 rs1466535 Heterozygous (C/T)	0.93 (0.45-1.93)	0.84	57.5%	RE
LRP1 rs1466535 Homozygous (C/C)	0.85 (0.22-3.32)	0.81	87.8%	RE

LRP1 rs1466535 Additive (C Allele)	1.09 (1.00-1.19)	0.047	69.5%	RE
**LRP1* rs1466535 Additive (C Allele)	1.15 (1.10-1.21)	$2.5x10^{-10}$	0.0%	FE
MMP2 rs243865 Heterozygous (C/T)	0.87 (0.60-1.24)	0.43	73.7%	RE
MMP2 rs243865 Homozygous (T/T)	0.65 (0.46-0.93)	0.02	0%	FE
MMP2 rs243865 Dominant (C/T & T/T)	0.82 (0.60-0.15)	0.25	70.9%	RE
MMP3 rs3025058 Heterozygous (6A/5A)	0.84 (0.70-1.02)	0.08	0.0%	FE
MMP3 rs3025058 Homozygous (6A/6A)	0.61 (0.49-0.76)	$1.6x10^{-5}$	0.0%	FE
MMP9 rs3918242 Heterozygous (C/T)	1.05 (0.92-1.18)	0.48	21.4%	FE
MMP9 rs3918242 Homozygous (T/T)	0.81 (0.49-1.33)	0.41	35.4%	RE
**MMP9* rs3918242 Heterozygous (C/T)	1.08 (0.91-1.27)	0.40	30.7%	RE
**MMP9* rs3918242 Homozygous (T/T)	0.93 (0.61-1.42)	0.75	0%	FE
MMP13 rs2252070 Heterozygous (A/G)	1.08 (0.90-1.29)	0.41	0.0%	FE
MMP13 rs2252070 Homozygous (G/G)	1.16 (0.76-1.77)	0.48	50.7%	RE
MTHFR1 rs1801133 Heterozygous (C/T)	1.06 (0.87-1.30)	0.57	68.6%	RE
MTHFR1 rs1801133 Homozygous (T/T)	1.06 (0.81-1.40)	0.66	60.7%	RE
**MTHFR1* rs1801133 Heterozygous (C/T)	1.07 (0.85-1.36)	0.56	72.3%	RE
**MTHFR1* rs1801133 Homozygous (T/T)	0.96 (0.75-1.21)	0.70	37.1%	RE
NOS3 rs1799983 Heterozygous (G/T)	1.14 (0.84-1.55)	0.39	29.9%	RE
NOS3 rs1799983 Homozygous (T/T)	1.16 (0.52-2.58)	0.71	87.9%	RE
PHACTR1 rs12526453 Additive (C allele)	1.02 (0.86-1.22)	0.80	63.7%	RE
SERPINE1 rs1799889 Heterozygous (4G/5G)	0.90 (0.65-1.24)	0.51	0%	FE
SERPINE1 rs1799889 Homozygous (5G/5G)	1.10 (0.72-1.69)	0.66	0%	FE
**SERPINE1* rs1799889 Heterozygous (4G/5G)	0.92 (0.62-1.38)	0.62	0%	FE
**SERPINE1* rs1799889 Homozygous (5G/5G)	1.19 (0.70-2.03)	0.52	0%	FE
SORT1 rs599839 Additive (G Allele)	0.82 (0.77-0.86)	$2.6x10^{-13}$	0.0%	FE
TGFBR2 rs1036095 Heterozygous (C/G)	1.23 (0.83-1.81)	0.31	83.1%	RE
TGFBR2 rs1036095 Homozygous (G/G)	1.69 (0.76-3.77)	0.20	88.5%	RE
TGFBR2 rs764522 Heterozygous (C/G)	1.35 (0.91-1.99)	0.13	79.9%	RE
TGFBR2 rs764522 Homozygous (G/G)	1.73 (0.78-3.85)	0.18	86.2%	RE

TRIB1 rs2954029 Additive (A Allele)	1.06 (0.90-1.24)	0.45	59.0%	RE

* Sensitivity Analysis conducted with exclusion of studies because of deviation from HWE or an extreme outlying result

OR, Odds Ratio; RE, Random Effects Meta-analysis; FE, Fixed Effects Meta-analysis

Table 4. Assessment of Evidence of Association

Gene	Polymorphism	Amount of Evidence	Replication	Protection from Bias	Overall Assessment
3p21	rs7635818	A	C	C	Weak
9p21	rs10757278	A	A	A	**Strong**
ACE	rs4646994	A	A	C	Weak
AGTR1	rs5186	A	B	B	**Moderate**
APOA1	rs964184	A	C	C	Weak
APOE	rs439401	A	C	C	Weak
APOB	rs1367117	A	C	C	Weak
CCR5	rs333	B	C	C	Weak
CRP	rs3091244	A	C	C	Weak
DAB2IP	rs7025486	A	A	A	**Strong**
ELN	rs2071307	B	C	C	Weak
HLA-A	A2	C	C	C	Weak
HLA-B	B61	C	C	C	Weak
HMOX1	GT(n)	C	C	C	Weak
IL6R	rs7529229	A	A	A	**Strong**
IL10	rs1800896	B	C	B	Weak
LDLR	rs6511720	A	B	A	**Moderate**
LPA	rs10455872	A	A	A	**Strong**
LRP1	rs1466535	A	A	A	**Strong**
MMP2	rs243865	B	C	B	Weak
MMP3	rs3025058	A	A	B	**Moderate**
MMP9	rs3918242	B	C	C	Weak
MMP13	rs2252070	C	C	C	Weak
MTHFR1	rs1801133	B	C	C	Weak
NOS3	rs1799983	B	C	B	Weak
PLA2G7	rs16874954	B	C	C	Weak
PHACTR1	rs12526453	A	C	C	Weak
SERPINE1	rs1799889	A	C	C	Weak
SORT1	rs599839	A	A	A	**Strong**
TGFBR1	rs10819634 rs1571590 rs1626340	A	C	C	Weak
TGFBR2	rs1036095 rs764522	A	C	B	Weak
TIMP1	rs4898	C	C	C	Weak
TIMP2	nt573 G/A	C	C	C	Weak
TRIB1	rs2954029	A	C	C	Weak

Figures

Legend to Figure 1: PRISMA flowchart for Systematic Review

Legend to Figure 2: Study frequency and median study size, 1994-2014

Supplementary Tables

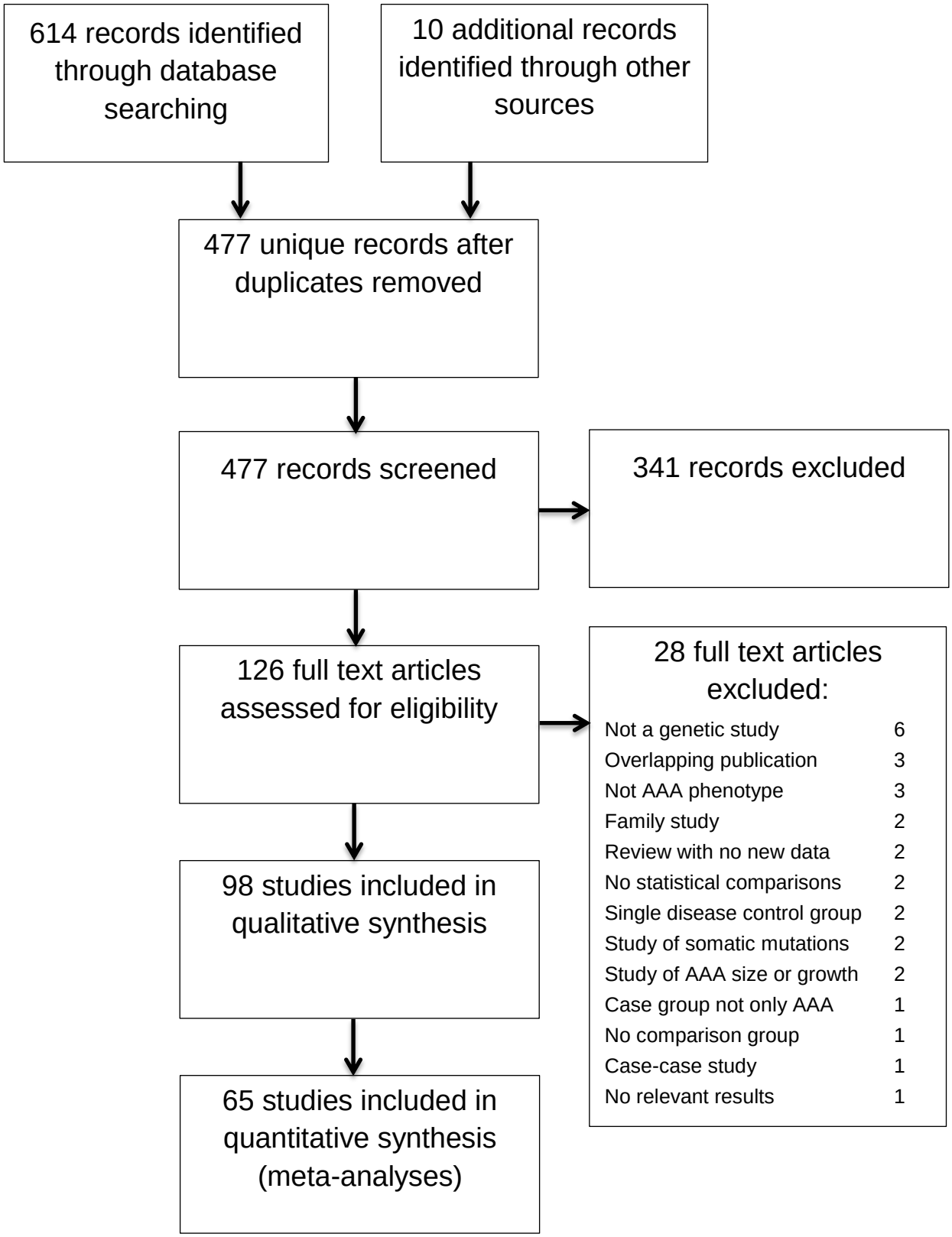
Supplementary Table 1: Excluded studies and reasons for exclusion

Supplementary Table 2: Characteristics of included studies

Supplementary Table 3: Number of reports in which genes were investigated in candidate gene studies (including genetic risk score studies)

Supplementary Table 4. Gene regions for which meta-analysis was not possible

Supplementary Table 5. Meta-analyses of odds ratios for associations between genetic variants and AAA.


614 records identified through database searching
10 additional records identified through other sources
477 unique records after duplicates removed
477 records screened
341 records excluded
126 full text articles assessed for eligibility
28 full text articles excluded:
Not a genetic study 6
Overlapping publication 3
Not AAA phenotype 3
Family study 2
Review with no new data 2
No statistical comparisons 2
Single disease control group 2
Study of somatic mutations 2
Study of AAA size or growth 2
Case group not only AAA 1
No comparison group 1
Case-case study 1
No relevant results 1
98 studies included in qualitative synthesis
65 studies included in quantitative synthesis (meta-analyses)